

1. A yeast cell comprising an expression construct comprising a nucleic acid  
encoding a protein comprising an alpha synuclein, wherein the expression construct is  
integrated in the genome of the yeast cell, and wherein expression of the nucleic acid is  
regulated by an inducible promoter, such that induction of production of the protein is  
5 toxic to the yeast cell.

2. The yeast cell of claim 1, wherein the cell comprises two integrated copies of  
the expression construct.

10 3. The yeast cell of claim 1, wherein induction of expression of the nucleic acid  
renders the cell non-viable.

4. The yeast cell of claim 1, wherein induction of expression of the nucleic acid  
arrests growth of the cell.

15 5. The yeast cell of claim 1, wherein the alpha synuclein is human alpha synuclein.

6. The yeast cell of claim 1, wherein the alpha synuclein is a mutant alpha-  
synuclein.

20 7. The yeast cell of claim 1, wherein the yeast is *Saccharomyces cerevisiae*,  
*Saccharomyces uvae*, *Saccharomyces kluyveri*, *Schizosaccharomyces pombe*,  
*Kluyveromyces lactis*, *Hansenula polymorpha*, *Pichia pastoris*, *Pichia methanolica*, *Pichia*  
kluyveri, *Yarrowia lipolytica*, *Candida* sp., *Candida utilis*, *Candida cacaoi*, *Geotrichum* sp.,  
25 or *Geotrichum fermentans*.

8. The yeast cell of claim 1, wherein the inducible promoter is GAL1-10, GAL1,  
GALL, GALS, GPD, ADH, TEF, CYC1, MRP7, MET25, TET, VP16, or VP16-ER.

9. The yeast cell of claim 1, wherein the expression construct is an integrative plasmid.

10. The yeast cell of claim 9, wherein the integrative plasmid is pRS303, pRS304,  
5 pRS305, or pRS306.

11. The yeast cell of claim 1, wherein the protein is a fusion protein comprising a detectable protein.

10 12. The yeast cell of claim 11, wherein the detectable protein is a fluorescent protein, an enzyme, or an epitope.

13. The yeast cell of claim 12, wherein the detectable protein is a fluorescent protein selected from the group consisting of a red fluorescent protein, green fluorescent  
15 protein, blue fluorescent protein, yellow fluorescent protein, and cyan fluorescent protein.

14. The yeast cell of claim 1, wherein at least one gene that encodes a polypeptide involved in drug efflux or cell permeability is disrupted.

20 15. The yeast cell of claim 14, wherein the at least one gene is PDR1, PDR3, or ERG6.

16. The yeast cell of claim 14, wherein the at least one gene is PDR5.

25 17. A yeast cell expressing a toxicity-inducing amount of a protein comprising an alpha synuclein.

18. The yeast cell of claim 17, wherein the cell comprises an integrated expression construct comprising a nucleic acid encoding the protein.

19. The yeast cell of claim 17, wherein the cell comprises two integrated copies of an expression construct comprising a nucleic acid encoding the protein.

20. The yeast cell of claim 17, wherein the alpha synuclein is human alpha  
5 synuclein.

21. The yeast cell of claim 17, wherein the alpha synuclein is a mutant alpha-synuclein.

10 22. The yeast cell of claim 17, wherein the yeast is *Saccharomyces cerevisiae*, *Saccharomyces uvae*, *Saccharomyces kluyveri*, *Schizosaccharomyces pombe*, *Kluyveromyces lactis*, *Hansenula polymorpha*, *Pichia pastoris*, *Pichia methanolica*, *Pichia kluyveri*, *Yarrowia lipolytica*, *Candida* sp., *Candida utilis*, *Candida cacaoi*, *Geotrichum* sp., or *Geotrichum fermentans*.

15 23. A method of identifying a compound that prevents or suppresses alpha-synuclein-induced toxicity, the method comprising:  
culturing the yeast cell of claim 1 in the presence of a candidate agent and under conditions that allow for expression of the protein at a level that, in the absence of the

20 candidate agent, is sufficient to induce toxicity in the yeast cell; and

determining whether toxicity in the yeast cell is less in the presence of the candidate agent as compared to in the absence of the candidate agent,

25 wherein if the toxicity is less in the presence of the candidate agent, then the candidate agent is identified as a compound that prevents or suppresses alpha-synuclein-induced toxicity.

24. The method of claim 23, wherein the alpha synuclein is human alpha synuclein.

25. The method of claim 23, wherein the alpha synuclein is a mutant alpha-synuclein.
26. The method of claim 25, wherein the mutant alpha-synuclein is mutant human alpha-synuclein A53T.

27. A method of identifying an extragenic suppressor of alpha-synuclein-induced toxicity, the method comprising:

10 culturing the yeast cell of claim 1, wherein an endogenous gene of the yeast cell has been disrupted, under conditions that allow for expression of the protein at a level that, in the absence of the disruption of the endogenous gene, is sufficient to induce toxicity in the yeast cell; and

15 determining whether toxicity in the yeast cell is less in the presence of the disruption of the endogenous gene as compared to in the absence of the disruption of the endogenous gene,

wherein if the toxicity is less in the presence of the disruption of the endogenous gene, then the disrupted endogenous gene is identified as an extragenic suppressor of alpha-synuclein-induced toxicity.

20 28. A method of identifying a compound that modulates alpha-synuclein localization to a plasma membrane, the method comprising:

culturing, in the presence of a candidate agent, a yeast cell ectopically expressing a protein comprising an alpha-synuclein; and

25 determining whether localization of the protein to the plasma membrane in the yeast cell is altered in the presence of the candidate agent as compared to in the absence of the candidate agent,

wherein if localization of the protein to the plasma membrane is altered in the presence of the candidate agent, then the candidate agent is identified as a compound that modulates alpha-synuclein localization to the plasma membrane.

29. A method of identifying a compound that inhibits the aggregation or formation of inclusions of alpha-synuclein, the method comprising:

    culturing, in the presence of a candidate agent, a yeast cell ectopically expressing a protein comprising an alpha-synuclein; and

5     determining whether cytoplasmic aggregation or inclusion formation of the protein is less in the presence of the candidate agent as compared to in the absence of the candidate agent,

    wherein if aggregation or formation of inclusions of the protein is less in the presence of the candidate agent, then the candidate agent is identified as a compound that  
10     inhibits the aggregation or formation of inclusions of alpha-synuclein.

30. A method of identifying a compound that promotes disaggregation of alpha-synuclein, the method comprising:

    providing a yeast cell ectopically expressing a protein comprising an alpha-synuclein, wherein the cell comprises cytoplasmic aggregates or inclusions of the protein;  
15     contacting the yeast cell with a candidate agent; and  
    determining whether cytoplasmic aggregation or inclusion formation of the protein is reduced in the presence of the candidate agent as compared to in the absence of the candidate agent,

20     wherein if aggregation or formation of inclusions of the protein is reduced in the presence of the candidate agent, then the candidate agent is identified as a compound that promotes disaggregation of alpha-synuclein.

31. A method of identifying a compound that prevents or suppresses proteasomal impairment caused by alpha-synuclein, the method comprising:

    culturing, in the presence of a candidate agent, a yeast cell ectopically expressing a protein comprising an alpha-synuclein; and

    determining whether proteasomal impairment in the cell is less in the presence of the candidate agent as compared to in the absence of the candidate agent,

wherein if proteasomal impairment in the cell is less in the presence of the candidate agent, then the candidate agent is identified as a compound that prevents or suppresses proteasomal impairment caused by alpha-synuclein.

5        32. A method of identifying a compound that prevents or suppresses phospholipase D (PLD) inhibition caused by alpha-synuclein, the method comprising:

          culturing, in the presence of a candidate agent, a yeast cell ectopically expressing a protein comprising an alpha-synuclein; and

          determining whether PLD inhibition in the cell is less in the presence of the

10      candidate agent as compared to in the absence of the candidate agent,

          wherein if PLD inhibition in the cell is less in the presence of the candidate agent, then the candidate agent is identified as a compound that prevents or suppresses PLD inhibition caused by alpha-synuclein.

15        33. A method of identifying a compound that prevents or suppresses oxidative stress caused by alpha-synuclein, the method comprising:

          culturing, in the presence of a candidate agent, a yeast cell ectopically expressing a protein comprising an alpha-synuclein; and

          determining whether oxidative stress in the cell is less in the presence of the

20      candidate agent as compared to in the absence of the candidate agent,

          wherein if oxidative stress in the cell is less in the presence of the candidate agent, then the candidate agent is identified as a compound that prevents or suppresses oxidative stress caused by alpha-synuclein.

25        34. A method of identifying a compound that reduces or inhibits an interaction of alpha-synuclein with an alpha-synuclein associated protein, the method comprising:

          culturing, in the presence of a candidate agent, a yeast cell ectopically expressing (i) a first protein comprising an alpha-synuclein, and (ii) a second protein comprising an alpha-synuclein associated protein; and

determining whether the interaction between the first protein and the second protein in the cell is less in the presence of the candidate agent as compared to in the absence of the candidate agent,

5 wherein if the interaction between the first protein and the second protein in the cell is less in the presence of the candidate agent, then the candidate agent is identified as a compound that reduces or inhibits the interaction of alpha-synuclein with the alpha-synuclein associated protein.

10 35. The method of claim 34, wherein the alpha-synuclein associated protein is dephospho-BAD, protein kinase C (PKC), mitogen-activated extracellular regulated kinase (ERK), synphilin-1, Huntington (htt), phospholipase D (PLD), or parkin.

15 36. The method of claim 34, wherein the alpha-synuclein associated protein is Tau.

20 37. A method of identifying an alpha-synuclein associated protein, the method comprising:

transforming a yeast cell with (i) a first expression construct encoding a first protein comprising an alpha-synuclein, and (ii) a second expression construct encoding a second protein comprising a candidate protein;

25 incubating the yeast cell under conditions that allow for expression of the first protein and the second protein; and

determining whether the first protein interacts with the second protein, wherein if an interaction occurs, the candidate protein is identified as an alpha-synuclein associated protein.

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38. A method of identifying a gene that is involved in an alpha-synuclein associated disease, the method comprising:

isolating RNAs from a first yeast cell that ectopically expresses alpha-synuclein;

isolating RNAs from a second yeast cell that does not ectopically express alpha-

30 synuclein;

comparing the RNAs isolated from the first yeast cell and the RNAs isolated from the second yeast cell; and

identifying an RNA that is present at a higher or lower level in the first cell relative to the second yeast cell, to thereby identify a corresponding gene that is involved in an

5 alpha-synuclein associated disease.

39. The method of claim 38, wherein the RNA is identified by performing differential display.

10 40. The method of claim 38, wherein the RNA is identified by performing subtractive hybridization.

15 41. A method of treating an individual suffering from a protein misfolding disease, the method comprising administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound identified by the method of claim 23.

20 42. A method of treating an individual suffering from Parkinson's Disease, the method comprising administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound identified by the method of claim 23.